Exhibit 14

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Review

Magnetic Resonance Imaging of Short T_2 Components in Tissue

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The most widely used clinical magnetic resonance imaging techniques for the diagnosis of parenchymal disease employ heavily T_2-weighted sequences to detect an increase or decrease in the signal from long T_2 components in tissue. Tissues also contain short T_2 components that are not detected or only poorly detected with conventional sequences. These components are the majority species in tendons, ligaments, menisci, periosteum, cortical bone and other related tissues, and the minority in many other tissues that have predominantly long T_2 components.

The development and clinical application of techniques to detect short T_2 components are just beginning. Such techniques include magic angle imaging, as well as short echo time (TE), and ultrashort TE (Ute) pulse sequences. Magic angle imaging increases the T_2 of highly ordered, collagen-rich tissues such as tendons and ligaments so signal can be detected from them with conventional pulse sequences. Ute sequences detect short T_2 components before they have decayed, both in tissues with a majority of short T_2 components and those with a minority. In the latter case steps usually need to be taken to suppress the signal from the majority of long T_2 components. Fat suppression of different types may also be helpful. Once signal from short T_2 components has been detected, different pulse sequences can be used to determine increases or decreases in T_1 and T_2 and study contrast enhancement.

Using these approaches, signals have been detected from normal tissues with a majority of short T_2 components such as tendons, ligaments, menisci, periosteum, cortical bone, dentine and enamel (the latter four tissues for the first time) as well as from the other tissues in which short T_2 components are a minority. Some diseases such as chronic fibrosis, gliosis, haemorrhage and calcification may increase the signal from short T_2 components while others such as loss of tissue, loss of order in tissue and an increase in water content may decrease them. Changes of these types have been demonstrated in tendonopathy, intervertebral disc disease, ligament injury, haemachromatosis, pituitary perivascular fibrosis, gliomas, multiple sclerosis and angiomas.

Use of these techniques has reduced the limit of clinical detectability of short T_2 components by about two orders of magnitude from about 10 ms to about 100 μs. As a consequence it is now possible to study tissues that have a majority of short T_2 components with both "bright" and "dark" approaches, with the bright (high signal) approach offering options for developing tissue contrast of different types, as well as the potential for tissue characterization. In addition, tissues with a minority of short T_2 components may demonstrate changes in disease that are not apparent with conventional heavily T_2-weighted sequences. Gatehouse, P. D. and Bydder, G. M. (2003). *Clinical Radiology* **58**, 1–19.

Key words: magnetic resonance imaging, short T_2 components, ultrashort echo times.

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INTRODUCTION

The most common method for diagnosing parenchymal disease in clinical magnetic resonance (MR) imaging involves

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the use of heavily T_2-weighted sequences to detect an increase or decrease in long T_2 components in tissue. This approach has been successful for over 20 years, and encompasses conventional spin-echo sequences, as well as newer developments such as fast spin-echo imaging, fluid attenuated inversion recovery (FLAIR), clinical EPI, diffusion-weighted imaging and susceptibility weighted imaging (Fig. 1).

In addition to long T_2 components, tissues contain short T_2 components. In some tissues such as tendons, ligaments, menisci and cortical bone these are the majority species. Conventional clinical methods are insensitive to these components, and so these tissues typically have a low or zero signal intensity with all pulse sequences (Fig. 2*a*). They include tissues that are virtually always of zero signal intensity (e.g. periosteum, cortical bone, dentine, enamel) and others in which a signal may be detectable depending on the pulse sequence used (e.g. meninges, falx) (Table 1). The lack of signal is useful diagnostically to provide a dark background against which high- signal abnormalities can be recognized, but it has meant that the options for developing tissue contrast of different types have been limited, and that these tissues have been poorly characterized in MR terms because there has been little or no signal available to manipulate with different pulse sequences.

Other tissues besides tendons, ligaments and related tissues contain short T_2 components but as a minority species (Fig. 2*b*). These components typically arise from protons in water closely associated with macromolecules (or protons actually within macromolecules) in cell membranes and intracellular structures, and are found to some extent in all tissues. Signals from these sources are not usually detected, or poorly detected with conventional pulse sequences.

To place these observations in a quantitative context, it has generally been thought that conventional clinical MR imaging does not detect signals from tissues with T_2s less than 10 ms [1]. Protons in water associated with macromolecules have T_2s less than 1 ms and protons in water very closely associated with macromolecules, or actually within macromolecules, have T_2s of about 10 μs [1].

Although those working in solid-state imaging are familiar with the problems of detecting signals from materials with a very short T_2s, there has been little clinical work performed in this area. Over the last decade less than 20 patients have been reported using techniques that specifically detect short T_2 components, and no patient studies have been described in major areas of clinical interest such as the brain, liver, pelvis and spine.

This paper describes approaches to detecting and characterizing short T_2 components in tissues for clinical purposes.

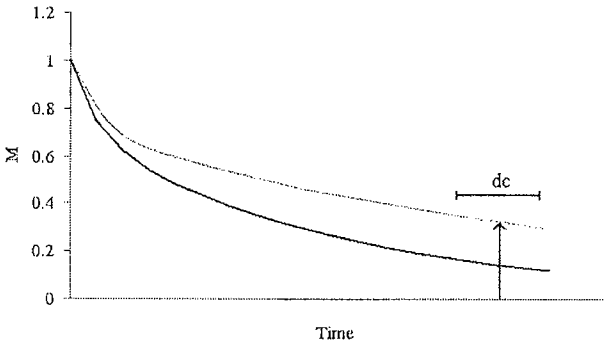


Fig. 1 – T_2 dependent decay of tissue magnetization and detection of long T_2 components. The decay for a normal tissue is shown in the lower curve and that for a tissue with an increased T_2 in the upper curve. The data collection (dc) is shown. The signal intensity in a voxel is proportional to the height of the signal during the data collection (vertical arrow) at the echo time (TE). A higher signal than in normal tissue is present in the abnormal tissue during the data collection which is obtained with a long TE.

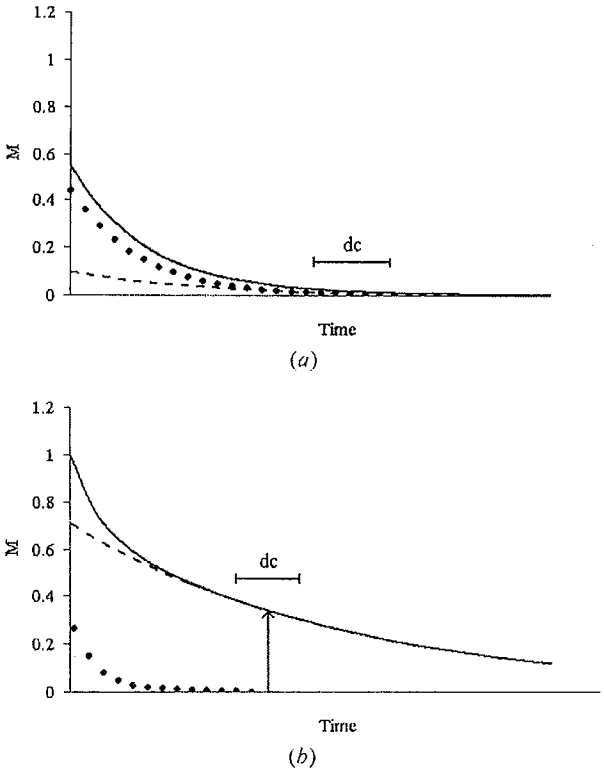


Fig. 2 – Magnetization decay (solid line) in a tissue with a majority of short T_2 components. The circles represent the short T_2 components which decay rapidly. In (a) the long T_2 components (dashed lines) are present in a much lower concentration and decay more slowly. At the data collection (dc) with an intermediate TE there is little or no signal. Magnetization decay (solid line) in a tissue with a minority of short T_2 components is shown in (b). The short T_2 components (circles) decay rapidly and give no signal. The detected signal comes from the long T_2 components (dashed line).

Table 1 – Tissues with a majority of short T_2 components

Short and very short T_2s (usually zero signal with conventional pulse sequences)	Moderately short T_2s (usually zero or low signal with conventional pulse sequences)
Tendons (most)	Retinaculi (some)
Ligaments (most)	Fasciae (some)
Menisci	Bands (some)
Labri	Septa (some)
Periosteum	Membranes (some)
Cortical bone	Capsules (some)
Dentine	Meninges
Enamel	Falx

CHANGES IN DISEASE

A variety of pathological processes may increase or decrease the signal from short T_2 components. Increases are likely in fibrosis (especially if chronic), gliosis, phases of haemorrhage, calcification and increased iron deposition. Decreases in short T_2 component signals are likely with loss of tissue, loss of order in tissue, demyelination and oedema (with shift of short T_2 components to become long T_2 components).

Where there is no change apparent with conventional long T_2 component approaches, abnormalities may be apparent with short T_2 approaches in situations where spectroscopy or other techniques have suggested disease is present.

In general terms, contrast enhancement has previously only been detectable in tissues such as tendons and ligaments with a majority of short T_2 components in abnormal areas which have an increased T_2 so there is scope to apply contrast agents more widely. In tissues with a minority of short T_2 components, contrast enhancement may differ from that with conventional approaches based on detection of long T_2 components.

EXAMPLES

Examples involving normal and diseased tissues with a majority of short T_2 components followed by those with a minority are illustrated: Fig. 15 shows conventional T_2 weighted (*a*) and Flute (*b*) images in a case of mild disc bulging at L4/L5. At the posterior aspect of the disc there is a high signal intensity region consistent with localized scar formation (*b*). This is not apparent on the conventional T_2 weighted image.

Fig. 16 shows a d Cute image with high signal from the meniscus and two separate layers apparent in articular cartilage. Spectroscopic broad lines associated with deep articular cartilage and narrow lines associated with the superficial layer have previously been shown [25,26]. This image demonstrates the two different layers directly.

Fig. 17 shows sagittal scans of the knee after gadolinium chelate enhancement Fute images in a patient with a 15 month history of a severe skiing injury. High signal is seen in the patellar tendon (arrow) and posterior cruciate ligament (arrow).

A transverse image through the tibia with a d Fute image taken with a surface coil adjacent to the tibia shows high signal from the cortex in Fig. 18. The cortex has a T_2 of about 250 μs [27]. The signal is probably coming from collagen type I and bound water. Signal has not previously been detected from normal cortical bone in volunteers or patients.

The periodontal ligament is seen in Fig. 19*a*. It has not previously been recognized as a separate structure with MR imaging. The difference images show a moderately high signal from dentine and a low signal from enamel (Fig. 19*b*). With an anterior surface coil, high signal is seen from dentine and lower signal is seen from enamel in Fig. 19*c*. The difference image derived from Fig. 19*c* and a later echo shows equal signal levels for dentine and enamel consistent with more rapid decay in signal from the lower signal level in enamel (Fig. 19*d*). *In vitro* studies have shown that dentine has multi-component T_2s with a mean T_2 of about 200 μs [28] and enamel has a mean T_2 of about 60 μs [29] depending on the type of tissue preparation.

The median nerve displays a marked magic angle effect probably as a consequence of its high content of linear collagen fibres (Fig. 20). This effect has not previously been recognized with MR neurography. It is a potential source of confusion if increased signal is regarded as a marker of disease irrespective of tendon orientation to Bo.

High signal is seen in the synovium on the sagittal Fute images in chronic arthritis. This is probably due to chronic fibrosis with the fibrotic tissue having a short T_2 and relatively short T_1 (Fig. 21).

A very large fibroid has a high signal from short T_2 components and shows a signal greater than the normal uterus (Fig. 22).

In a case of haemachromatosis a uniform high signal in seen in the liver on the first echo (Fig. 23*a*) with marked loss of signal on the second echo at 2.13 ms (Fig. 23*b*).

The pituitary gland is shown in a normal female age 24 years in Fig. 24*a*. As expected, the posterior pituitary has a higher signal than the anterior pituitary on the T_1-weighted Fute

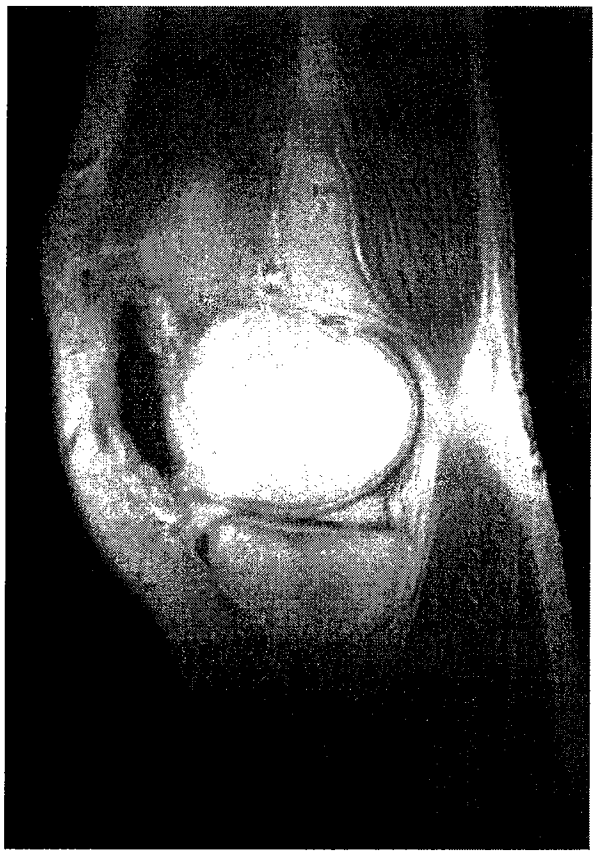
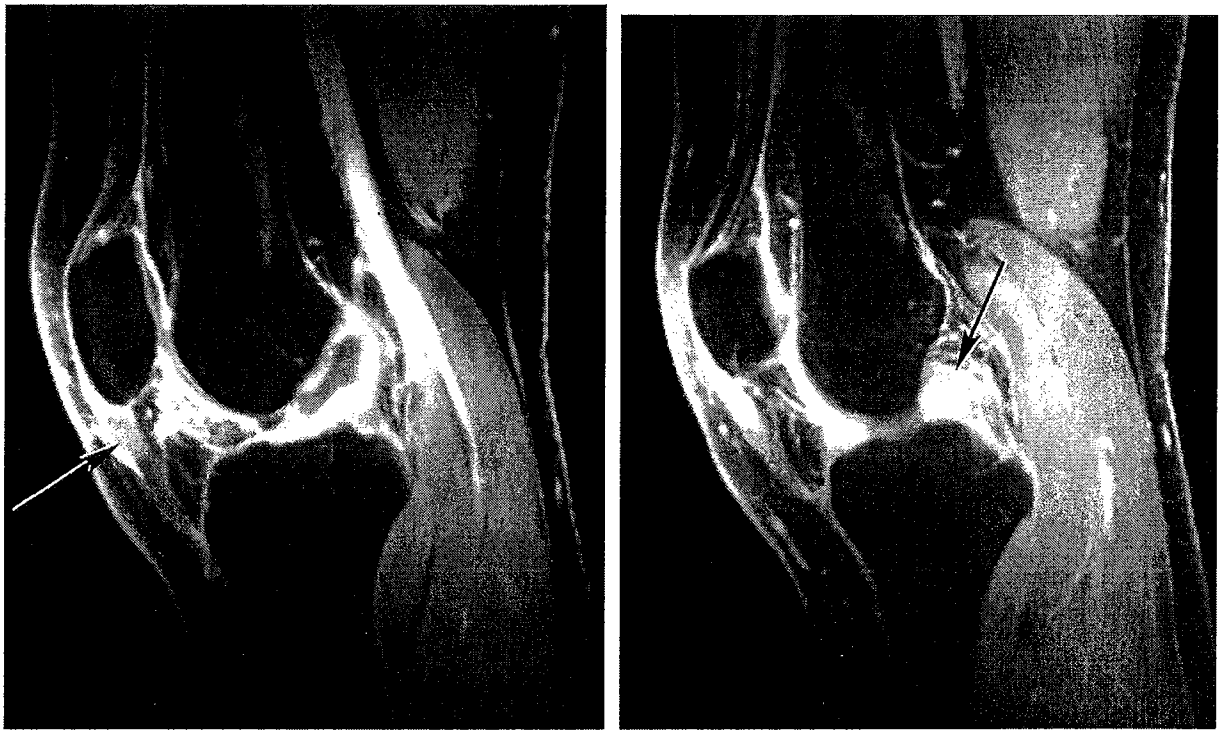


Fig. 16 – Sagittal image of the meniscus and articular cartilage. d Cute (TR/TE = 500/0.08 – TR/TE = 500/5.95 ms). The meniscus has a high signal and the articular cartilage has two layers, a high signal (high short T_2 components) deep layer, and a low signal superficial layer (low short T_2 components and high long T_2 components).



(*a*) (*b*)

Fig. 17 – Sagittal post-enhancement images of the patellar tendon and posterior cruciate ligament. Fute (TR/TE = 500/0.08 ms) images of the knee 18 months after injury. The patellar tendon shows a region of high signal (arrow, *a*) as does the antero–superior aspect of the posterior cruciate ligament (arrow, *b*).

image. In a normal male volunteer aged 58 years examined with the same sequence, high signal is seen in a thick rim around both the anterior and posterior pituitary and the gland is smaller in size. The features are probably due to perivascular fibrosis which is seen with increasing frequency into the tenth decade in post-mortem studies [30]. It is associated with a decrease in somatotrophs. The condition has not previously been recognized with CT or MR imaging.

Fig. 25 is a normal Stute image of the brain obtained from images with TEs of (*a*) 0.08 ms and (*b*) 5.95 ms. The long T_2 components from white matter have been nulled. The difference image (*c*) shows high signal from the normal white matter in the centrum semiovale.

Fig. 26 is from a patient treated for glioma in the left frontal region. There is loss of short T_2 components evident in Fig. 26*b* beyond the region of abnormality shown in Fig. 26*a*.

Fig. 27 is a 46 year old patient 4 years after treatment of a high-grade glioma with surgery, radiotherapy and chemotherapy with a good result. The d Cute (*b*) image shows multiple angiomas (short arrows) which are not apparent on the conventional T_2-weighted image (*a*). (A single large angioma was visible with both conventional and d Cute imaging at a higher level.) The tumour also has a high signal margin probably due to gliosis (long arrow) although this region is isointense on the conventional heavily T_2-weighted image.

Fig. 28 is from a 39 year old woman with a 9 year history of multiple sclerosis. Loss of short T_2 components is apparent in the central white matter. The loss of signal from short T_2 components extends beyond that of many of the lesions seen on the heavily T_2-weighted sequence. Normal short T_2 component signal is only apparent towards the periphery of the hemispheres. In multiple sclerosis a reduction in short T_2 components has been shown in fixed specimens of brain [16,31].

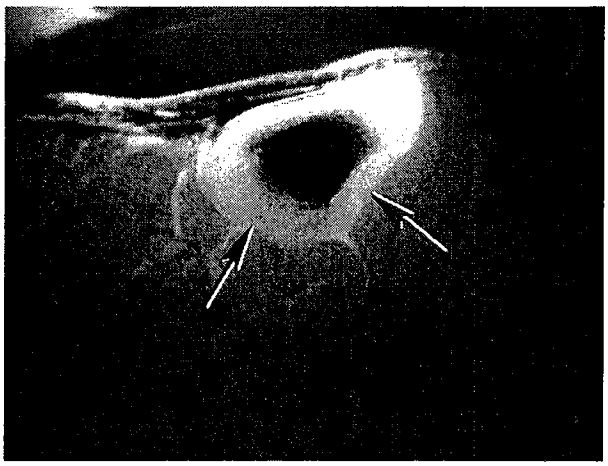


Fig. 18 – Cortex of the tibia. Transverse d Fute (TR/TE = 500/0.08 ms – TR/TE = 500/2.87 ms) image of the normal tibia obtained with a surface coil. Signal is quite obvious in the cortex of the tibia (arrows). It decreases with distance from the surface coil.